EXHIBIT B

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Modeling Parkinson's Disease

Parkinson's disease (PD) is a chronic, progressive, age-related, neurodegenerative disorder that affects over one million persons in the United States. The disease is characterized by degeneration of dopamine neurons in the substantia nigra pars compacta coupled with alpha-synuclein–positive inclusions (Lewy bodies) and processes (Lewy neurites). Neurodegeneration with Lewy pathology is also found within norepinephrine-containing neurons of the locus coeruleus, cholinergic neurons of the nucleus basalis of Meynert, serotonin-ergic neurons of the dorsal raphe, and selected neurons in the olfactory system, cerebral hemispheres, upper and lower brain stem, spinal cord, and peripheral autonomic nervous system. Current therapies are primarily based on a dopamine replacement strategy, and fail to address those features caused by nondopaminergic pathology or the inexorable progression of the disease. As a consequence, most patients eventually experience intolerable disability that cannot be fully controlled with current therapies. A neuroprotective therapy that slows or stops disease progression is the single most important unmet medical need in PD. However, accomplishing that goal has proven difficult to achieve. One of the major obstacles is a model that reflects the etiopathogenesis of the disease and replicates its widespread pathology and progressive behavioral course in which to test putative neuroprotective interventions preclinically. Indeed, there are numerous examples of

promising agents that have shown protective effects in the laboratory, but have failed to demonstrate benefits in clinical trials.[1] While there are several critical factors that might contribute to this dilemma such as incorrect dosing and inadequacy of clinical endpoints, we believe the lack of a valid model is foremost.

In the present issue of *Annals*, Tinsley et al.[2] report that they can model the pathological overexpression of alpha-synuclein, complete with inclusion body formation in transgenic dopamine D2 receptor knockout mice. They also note evidence of increased dopamine turnover, oxidative stress, endoplasmic reticulum stress, and markers of apoptosis in dopamine neurons, all of which are found in PD. This model could thus be valuable for testing hypotheses related to alpha-synuclein accumulation, oxidative stress, and dopamine-related compensatory mechanisms in PD. However, there were no reported behavioral changes, there was no significant nigral nerve cell loss or loss of striatal dopamine, there was no evidence of degeneration or inclusion body formation in nondopaminergic areas affected in PD, and the initiating insult has dubious relevance to PD pathogenesis. For these reasons, this model will likely not prove useful for testing putative neuroprotective drugs. In this review we consider models of PD that are available for preclinical testing of candidate neuroprotective agents.

Classic Models

In vitro models, primarily using dopaminergic cell lines and primary mesencephalic cultures, have frequently been used to gain a preliminary assessment of the potential protective effects of a new intervention. These studies have proven useful for exploring possible mechanisms whereby a drug might confer protective effects, but these models that employ nonneuronal or embryonic cells are so far removed from PD that it is impossible to know if positive (or negative) results are relevant to the disease state.

The 6-hydroxydopamine (6-OHDA) rodent and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse and monkey models are the most widely used in vivo models for testing PD interventions, and no putative neuroprotective drug has gone for clinical testing in patients without positive results in one or more of these models. However, these models act acutely, primarily damage the dopamine system, and spare the nondopaminergic areas that degenerate in PD. The MPTP models have been demonstrated to accumulate alpha-synuclein within residual nigral perikarya.[3] However, for the most part, these neurons do not display frank Lewy bodies with beta-pleated sheets.[4] Further, there is no evidence to indicate that either of these toxins is relevant to the etiology or pathogenesis of cell death in PD. They have proven to be exquisitely useful models for testing the effects of dopamine depletion, but have been less valuable in predicting the results of putative neuroprotective therapies in PD.

Models of PD have also attempted to exploit pathogenic features implicated in PD. Postmortem studies provide evidence for involvement of oxidative stress, excitotoxicity, and inflammation. Converging pathologic and genetic evidence has also implicated mitochondrial dysfunction and the accumulation and misfolding of unwanted proteins as possible central features in the neurodegenerative process. These observations have formed the basis for many of the candidate neuroprotective drugs that have been tested in PD, but activation of these pathways with agents such as buthionine sulfoxamine to block glutathione, iron to promote free radical formation, or lipopolysaccharide to induce inflammation have not as yet generated a consistent and satisfactory model of PD for preclinical testing of new agents. Part of the problem is that these agents do not cross the blood brain barrier, and it is not clear which, if any, of these mechanisms is primary and drives the cell death process, or whether they are even directly related to the direct cause of neurodegeneration in PD.

Rotenone is a pesticide that has attracted particular attention because, like MPTP, it can selectively damage mitochondrial complex I in a pattern similar to what is found in PD. Initial studies indicated that rotenone administration to rodents induced degeneration of dopamine neurons coupled with inclusion bodies.[5] However, the toxin did not induce damage in areas that are affected in PD and caused degeneration in areas that are typically spared. Further, the toxin was associated with damage to peripheral organs leading to fatality in a large number of animals. Its value as a model of PD has been further limited by subsequent investigators having difficulty reproducing these results. Even in the best of hands, there has been considerable variability across animals in the capacity of rotenone to induce nigrostriatal degeneration, thus making its use for testing of putative neuroprotective agents problematic. More recent studies using refined protocols report consistent apomorphine responsive behavioral features with a loss of tyrosine hydroxylase (TH)-positive dopamine neurons and alpha-synuclein–positive inclusions.[6] It remains to be determined if this will now be a satisfactory model for preclinical testing of new agents for PD.

Proteasome inhibitors have been the source of much discussion. Proteasome inhibition impairs the clearance of unwanted proteins by the ubiquitin proteasome system and induce selective dopaminergic cell loss with alpha-synuclein–positive inclusion body formation in vitro.[7] Intrastriatal administration of proteasome inhibitors can cause nigrostriatal degeneration with inclusions in rats,[8] but systemic administration of proteasome inhibitors has not been established to be a valid

model of PD (eg, Ref. 9). More recently, a conditional knockout of a subunit of the 26S proteasome has been shown to impair ubiquitin-mediated protein degradation and to cause extensive degeneration of nigrostriatal neurons with Lewy-like inclusions.[10] Thus the creation of models based upon failed proteasomal function still warrants further inquiry. In addition, as alpha-synuclein is primarily cleared by the lysosome, models based on interruption of this system are also anxiously awaited.[11]

Genetic Models of PD

More promising are models based on gene mutations associated with familial forms of PD, as they reflect the etiopathogenesis of at least one form of the disease. Alpha-synuclein has attracted particular attention, as several mutations and both duplication and triplication of the wild-type protein have each been associated with familial PD.[12–14] The latter studies have particular importance as they indicate that just having too much of a normally expressed protein can cause PD. Further, aggregated alpha-synuclein is a major component of Lewy bodies, the pathologic hallmark of sporadic PD. Transgenic models have thus been anxiously awaited. Unfortunately, none of the transgenic alpha-synuclein models precisely replicate the neurodegenerative pattern or behavior of PD, and a variety of different phenotypes and pathologies can be seen with different promoters and transgenes.[15] This failure to replicate PD pathology may reflect differences in how alpha-synuclein is metabolized in rodents compared to humans. Thus, from a neuroanatomical and behavioral perspective, currently available transgenic alpha-synuclein models are not optimal. These models may, nonetheless, still be valuable for testing candidate neuroprotective drugs, as the pathogenic process leading to neurodegeneration may be the same in the animal model and PD even though it results in a different pathology.

An alternate way to induce overexpression of alpha-synuclein is with viral vector delivery to a specific target such as the substantia nigra. This strategy results in progressive behavioral changes and neuropathology that more closely mirrors PD, with degeneration of dopamine neurons and the formation of alpha-synuclein–positive inclusion bodies.[16] Interestingly, glial cell–derived neurotrophic factor (GDNF), a trophic factor that failed to provide benefits to PD patients in a double-blind trial, also failed to provide benefit in this model,[17] suggesting that it may more accurately predict clinical results than more traditional models which show a dramatic improvement with trophic factors.

Initial transgenic models that knocked out or carried a mutant form of Parkin were disappointing and did not replicate PD pathology or behavior.[18,19] However, Lu et al.[20] developed a bacterial artificial chromosome (BAC) transgenic mouse model expressing a C-terminal truncated human mutant parkin (Parkin-Q311X) in dopamine neurons driven by a dopamine transporter promoter. Parkin-Q311X mice exhibited multiple late-onset and progressive hypokinetic motor deficits. Stereological analyses revealed that the mutant mice developed age-dependent dopamine neuronal degeneration in the substantia nigra accompanied by a significant loss of terminals in the striatum. Neurochemical analyses reveal a significant reduction of striatal dopamine, which correlated with their hypokinetic motor deficits. Finally, mutant Parkin-Q311X mice, but not wild-type controls, exhibited age-dependent accumulation of proteinase K-resistant alpha-synuclein in substantia nigra neurons. This model is obviously worth further pursuit.

The Pitx3-deficient *aphakia* (*ak*) mice are gaining interest in the scientific community for modeling nigrostriatal degeneration in PD.[21] Unlike most other transgenic mouse models, close to 90% of dopaminergic neurons degenerate in this model. Moreover, motor deficits are reversed following administration of levodopa. Interestingly, these mice are impaired on a series of striatal-dependent, but not striatal-independent, tasks of learning and memory. A drawback to this model is that these mutants are blind and a blind control group is requited to intetptet behaviotal findings

The recent report of an transgenic animal model of PD that carries the $LRRK2^{R1441G}$ mutation (PARK 8) has attracted considerable interest,[22] as this mutation appears to be the most common cause of familial PD and has been identified in cases in older individuals with clinical and pathological features identical to sporadic PD. It is thus possible that the pathogenesis of cell death caused by this mutation is televant to many cases of so-called sporadic PD. LRRK2 mutant mice demonstrated age-dependent bradykinesia and akinesia that could be reversed with levodopa or apomorphine. Microdialysis performed in the presence of nomifensine revealed diminished striatal dopamine release. Histologically, there was a reduction in size of substantia nigra zona compacta (SNc) TH-positive neurons, and axons were beaded/fragmented and exhibited spheroids and dystrophic neurites. However, there was no significant loss of TH-positive dopamine neurons in the SNc, TH staining in the striatum was normal, and the status of nondopaminergic areas affected in PD are not described. Thus, it is too early to assume that this will be the definitive model of PD for screening new interventions.

Aging Models

Finally, aging is the best defined risk factor for PD, and might also serve as a model of the disease. Aging is associated with increased levels of oxidized proteins, impaired proteasomal function, alpha-synuclein accu-

Table. **Desirable Characteristics of an Optimal Model of PD**

Chronic progressive, levodopa responsive, motor features (ie, bradykinesia)
Degeneration of SNc dopamine neurons coupled with alpha synuclein positive inclusion bodies
Neurodegeneration with inclusions in nondopaminergic regions affected in PD
Available in small animal model (e.g., *Drosophila, C. elegans*) for high throughput testing
Available in large animal model (e.g. primate) for formal behavioral and pathological testing

SNc = substantia nigra zona compacta; PD = Parkinson's disease.

mulation, and reduced TH staining in the striatum and in nigral neurons.[23] Indeed, more than 20% of neurologically intact elderly individuals have Lewy body pathology, suggesting the possibility that they have a preclinical form of PD.[24] These observations raise the possibility that naturally occurring age-related increases in protein accumulation and misfolding, could eventually lead to a state of proteolytic stress and neurodegeneration. It is thus reasonable to consider that aging itself might be a model of PD that could be used for testing candidate neuroprotective agents. Additionally, examining candidate agents in any of the above-described models in aged rather than younger animals may have greater predictive validity for what might occur in PD. Indeed, it is well established that the physiological response to various PD-related toxins such as MPTP is age-dependent, possibly because older animals have a reduced capacity to upregulate compensatory mechanisms. The lack of predictive validity seen with animal models to date may, to some degree, reflect the fact that new therapeutic agents are primarily tested in young animals that do not accurately reflect the PD state. The use of aged animals might increase the likelihood of obtaining results that better predict what will occur in PD patients.

In conclusion, the lack of an optimal animal model of PD (see Table 1.) has been an obstacle to the development of a neuroprotective therapy. There is, however, some optimism that this problem might be overcome with the development of novel transgenic models and perhaps even aging. These approaches needs to be further tested to determine if they provide consistent and reproducible models, and to determine if therapeutic results obtained in these models translate into comparable results in the clinic.

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Neuroradiological Diagnosis of Idiopathic Normal-Pressure Hydrocephalus: The Search for the Holy Grail

In this issue of the *Annals of Neurology*, Palm and coworkers[1] report on the development and use of a measure to quantify the disproportionate increase in ventricular volume relative to the cerebral parenchyma in the setting of a population-based study. As a surrogate for cerebral atrophy, they used the cerebrospinal fluid (CSF) sulcal volume. They found that the ratio of the ventricular CSF volume to sulcal CSF volume correlated with the degree of impairment in gait, cognitive function, and self-reported measures of bladder continence. The analysis did require specific input from a trained radiologist to demarcate ventricular boundaries.

Although this is not the first study to try and quantify the significance of CSF volumes in different compartments, it is the first study to apply these methods to a population-based study. The authors found a strong association between the ratio of ventricular volumes to sulcal CSF volumes and gait and cognitive dysfunction. When such volumetric measures were used in retrospect in the past to discriminate patients with typical symptoms of normal-pressure hydrocephalus (NPH) into shunt responders versus nonresponders, they were found to be wanting.[2] It is possible that methodological differences and the variable selection of patients may account for the discrepancy in these results.

Although the association between gait dysfunction, cognitive and urinary impairment, and ventricular/sulcal volume is strong, we do not truly know whether these patients have NPH. Although no feature of gait is specific for NPH, using just impairment in one aspect of gait assessment (gait speed) as a surrogate marker is difficult to reconcile, because there are several potential causes of gait dysfunction in the elderly.

The greater prevalence of cognitive impairment as compared with gait dysfunction at each quartile analyzed also raises the possibility of other causative factors, because typically in NPH, gait impairment is supposed to be a cardinal manifestation. Although they did exclude patients with white matter disease and Alzheimer's disease, increases in ventricular volume have also been reported in patients with mild cognitive impairment due to neuro-degenerative diseases.

As Hakim and colleagues[3] and Adams and coauthors[4] have defined, gait dysfunction must be present in addition to impairment in either cognition or bladder function. We do see exceptions to this general rule, but these represent only a minority of the patients and would not be expected to be present disproportionately in this population-based study. Hence, although we enthusiastically support the quantitative measure as an objective and reliable way to assess ventricular volumes and its correlation with gait, cognitive dysfunction, and bladder dysfunction, the direct implication of a causative diagnosis of NPH is unjustified and deserves further study.

Thus, although the authors describe an association between volumetric measures and clinical parameters, no inferences can be made about the prevalence of NPH in this population-based study without further assessment.[1]

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